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FILE 'HOME' ENTERED AT 14:49:19 ON 06 AUG 2007

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                                                           ENTRY    SESSION
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DICTIONARY FILE UPDATES:   5 AUG 2007  HIGHEST RN 944042-79-9

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http://www.cas.org/support/stngen/stndoc/properties.html

=> E "AWD 131-138"/CN 25
E1            1     AWD 122-60/CN
E2            1     AWD 123-281/CN
E3            1 --> AWD 131-138/CN
E4            1     AWD 140-076/CN
E5            1     AWD 140-190/CN
E6            1     AWD 160-275/CN
E7            1     AWD 19-166/CN
E8            1     AWD 21-360/CN
E9            1     AWD 23-111/CN
E10           1     AWD 23-115/CN
E11           1     AWD 23-15/CN
E12           1     AWD 26-06/CN
E13           1     AWD 33-173/CN
E14           1     AWD 52-227/CN
E15           1     AWD 52-227 BITARTRATE/CN
E16           1     AWD 52-302/CN
E17           1     AWD 52-302 MONOTARTRATE/CN
E18           1     AWD 52-322/CN
E19           1     AWD 52-322 MONOTARTRATE/CN
E20           1     AWD 52-336/CN
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E23           1     AWD 52-362 BITARTRATE/CN
E24           1     AWD 52-365/CN
E25           1     AWD 52-365 BITARTRATE/CN

=> S E3
L1            1 "AWD 131-138"/CN
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=> DIS L1 1 IDE

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   188116-07-6  REGISTRY
ED   Entered STN:  10 Apr 1997
CN   2H-Imidazol-2-one, 1-(4-chlorophenyl)-1,5-dihydro-4-(4-morpholinyl)- (9CI)
     (CA INDEX NAME)
OTHER NAMES:
CN   AWD 131-138
CN   Imepitoin
MF   C13 H14 Cl N3 O2
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, EMBASE,
       IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, PHAR, PROUSDDR, SCISEARCH,
       SYNTHLINE, TOXCENTER, USPATFULL
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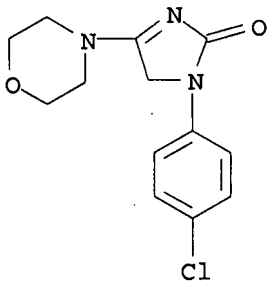


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

              10 REFERENCES IN FILE CA (1907 TO DATE)
              10 REFERENCES IN FILE CAPLUS (1907 TO DATE)


=> file caplus biosis medline embase
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   7.80       8.01

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=> s awd(a)131-138 or imepitoin or 188116-07-6
L2          51 AWD(A) 131-138 OR IMEPITOIN OR 188116-07-6

=> dup remove
ENTER L# LIST OR (END):l2
PROCESSING COMPLETED FOR L2
L3           28 DUP REMOVE L2 (23 DUPLICATES REMOVED)
                ANSWERS '1-14' FROM FILE CAPLUS
                ANSWERS '15-22' FROM FILE BIOSIS
                ANSWERS '23-24' FROM FILE MEDLINE
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ANSWERS '25-28' FROM FILE EMBASE

=> d ti au abs so py 1-10 l2

L2 ANSWER 1 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Synthesis, Pharmacology, and Structure-Activity Relationships of Novel Imidazolones and Pyrrolones as Modulators of GABAA Receptors
AU Grunwald, Christian; Rundfeldt, Chris; Lankau, Hans-Joachim; Arnold, Thomas; Hoefgen, Norbert; Dost, Rita; Egerland, Ute; Hofmann, Hans-Joerg; Unverferth, Klaus
AB New series of imidazolones and pyrrolones were synthesized. The compds. were tested for their anxiolytic properties due to modulation of the GABAA receptor response. Several derivs. exhibit considerable pharmacol. activity while lacking the typical side effects of benzodiazepine receptor agonists. 1-(4-Chlorophenyl)-4-morpholin-1-yl-1,5-dihydro-imidazol-2-one and 1-(4-chlorophenyl)-4-piperidin-1-yl-1,5-dihydro-imidazol-2-one were protective in the pentylenetetrazole test in rats with oral ED50 of 27.4 and 12.8 mg/kg and TD50 (rotarod) of >500 and 265 mg/kg, resp. The min. ED in the Vogel conflict test was 3 mg/kg for both compds. Common structure-activity relationship and comparative mol. field anal. models of the various series of derivs. could be established which are in accordance with a GABAA mediated pharmacol. action. The findings fit well into an established pharmacophore model. This model is refined by an addnl. steric restriction feature.
SO Journal of Medicinal Chemistry (2006), 49(6), 1855-1866
CODEN: JMCMAR; ISSN: 0022-2623
PY 2006

L2 ANSWER 2 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Anticonvulsant efficacy of the low-affinity partial benzodiazepine receptor agonist ELB 138 in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures
AU Loescher, Wolfgang; Potschka, Heidrun; Rieck, Susanne; Tipold, Andrea; Rundfeldt, Chris
AB Ataxia, sedation, amnesia, ethanol and barbiturate potentiation, loss of efficacy (tolerance), development of dependence, and the potential for drug abuse limit the clin. use of benzodiazepines (BZDs) for long-term treatment of epilepsy or anxiety. BZD ligands that are in current use act as full allosteric modulators of γ-aminobutyric acid (GABA)-gated chloride channels and, on long-term administration, trigger a functional uncoupling between the GABAA and BZD recognition sites. Partial allosteric modulators, which have a low intrinsic activity at the BZD recognition site of the GABAA receptor, might eventually overcome the limitations of full agonists such as diazepam (DZP). In the present study, the new low-affinity partial BZD-receptor agonist ELB 138 [former name AWD 131-138; 1-(4-chlorophenyl)-4-morpholino-imidazolin-2-one] was evaluated in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures. ELB 138 was shown to increase potently the pentylenetetrazole (PTZ) seizure threshold in dogs. Prolonged oral administration with twice-daily dosing of ELB 138 with either 5 or 40 mg/kg over a 5-wk period was not associated with loss of anticonvulsant efficacy in the PTZ dog model. To study whether phys. dependence developed during long-term treatment, the BZD antagonist flumazenil was injected after 5 wk of treatment with ELB 138. Compared with prolonged treatment with DZP, only relatively mild abstinence symptoms were precipitated in dogs treated with ELB 138, particularly at the lower dosage (5 mg/kg, b.i.d.). In a prospective trial in dogs with newly diagnosed epilepsy, ELB 138 markedly reduced seizure frequency and severity without significant difference to standard treatments (phenobarbital or primidone) but was much better tolerated than the standard drugs. In dogs with chronic epilepsy, most dogs exhibited a reduction in seizure frequency and severity during add-on treatment with ELB 138. The data demonstrate that the partial BZD receptor agonist ELB 138 exerts significant anticonvulsant efficacy without tolerance in a dog seizure model as well

as in epileptic dogs with spontaneously recurrent seizures. These data thus substantiate that partial agonism at the BZD site of GABAA receptors offers advantages vs. full agonism and constitutes a valuable approach for treatment of seizures.
SO Epilepsia (2004), 45(10), 1228-1239
CODEN: EPILAK; ISSN: 0013-9580
PY 2004

L2 ANSWER 3 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Use of dihydroimidazolones for the treatment of epilepsy in dogs
IN Rundfeldt, Chris; Dost, Rita; Loscher, Wolfgang; Tipold, Andrea; Unverferth, Klaus; Lankau, Hans-Joachim
AB The invention discloses the use of substituted dihydroimidazolones, particularly 1-(4-Chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (AWD 131-138) or a physiol. acceptable salt thereof for the treatment of epilepsy in dogs.
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2
PY 2004
2005
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L2 ANSWER 4 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Evaluation of the novel antiepileptic drug, AWD 131-138, for benzodiazepine-like discriminative stimulus and reinforcing effects in squirrel monkeys
AU Yasar, Sevil; Bergman, Jack; Munzar, Patrik; Redhi, Godfrey; Tober, Christine; Knebel, Norbert; Zschiesche, Michael; Paronis, Carol
AB AWD 131-138 {1-(4-chlorophenyl)-4-morpholino-imidazolin-2-one}, a new low-affinity partial benzodiazepine receptor agonist with potent anticonvulsant and anxiolytic properties in rodent models, was studied in squirrel monkeys trained to discriminate i.m. injections of midazolam (0.3 mg/kg) from injections of vehicle. Diazepam produced midazolam-like responding at cumulative doses of 1.0 and 3.0 mg/kg i.m. and decreased rates of responding at 3.0 mg/kg (plasma levels of about 400 ng/mL). In contrast, AWD 131-138 did not produce midazolam-like responding or alter response rates at cumulative doses up to 18.0 mg/kg i.m. (plasma levels over 2100 ng/mL). Other monkeys were trained to i.v. self-administer cocaine (56.0 μg/kg/injection). When AWD 131-138 (10-100 μg/kg/injection) was studied by substitution, responding declined to vehicle substitution levels within three sessions. At the dose of 100 μg/kg i.v. AWD 131-138, sufficient drug was self-administered during the first session (about 3.5 mg/kg) to produce plasma levels above 1000 ng/mL, yet responding over the next two sessions dropped to vehicle levels. The failure of AWD 131-138 to produce benzodiazepine-like discriminative effects and the absence of drug self-administration behavior when substituted for cocaine suggest that its abuse liability is low.
SO European Journal of Pharmacology (2003), 465(3), 257-265
CODEN: EJPHAZ; ISSN: 0014-2999
PY 2003

L2 ANSWER 5 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Analytical data and physicochemical properties of 1-(4-chlorophenyl)-4-morpholino-imidazolin-2-one, AWD 131-138
AU Heinecke, K.; Thiel, W.

AB The structure of the anticonvulsant 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazolin-2-one (Code: AWD 131-138, CAS-Number: 188116-07-6) was proved by IR, UV, 1H NMR, 13CNMR, and mass spectra. AWD 131-138 is practically insol. in a neutral aqueous medium at 20°C (S .apprx. 0.08 g/l). The solubility of the substance in 0.1 N HCl is about 2.7 g/l. In DMF, AWD 131-138 is sparingly soluble (S .apprx. 28.5 g/l). The pKa-value is about 2.5. The partition coeffs. P = COctanol/CWater at 37°C range from 0.7 at pH .apprx. 1 to about 20 at pH ≥6.

SO Pharmazie (2001), 56(6), 458-461
CODEN: PHARAT; ISSN: 0031-7144

PY 2001

L2 ANSWER 6 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI An assessment of rufinamide as an anti-epileptic in comparison with other drugs in clinical development

AU Jain, Kewal K.

AB A review with 28 refs. This article evaluates rufinamide, a new anti-epileptic drug (AED) in Phase III development. This review is done against the background of therapeutic challenges of epilepsy, old established AEDs, newly introduced AEDs and AEDs in clin. development. Pharmacol. properties of 12 AEDs in clin. trials (Phases I - III) are compared: ADCI, AWD 131-138, DP-VPA, ganaxolone, levetiracetam, losigamone, pregabalin, remacemide hydrochloride, retigabine, rufinamide, soretolide and TV1901. One of these, levetiracetam has been approved in the USA and is waiting approval in other countries. The protective index of rufinamide, as shown in rodent models of epilepsy, is much higher than that of most common AEDs. Features which make it a desirable AED are: (i) a broad spectrum of anti-epileptic actions including both partial and symptomatic generalized epilepsy; (ii) a statistically significant reduction in seizure frequency in clin. trials; (iii) efficacy and safety shown in a broad range of age groups including children and the elderly; (iv) rapid oral absorption enabling quick titration to ED and (v) a benign adverse event profile. Most of the events did not lead to discontinuation in clin. trials. These features offer considerable advantages over the existing anti-epileptic drugs. It is one of the two drugs in development which have reached Phase III and is expected to be approved by the year 2001 - 2002.

SO Expert Opinion on Investigational Drugs (2000), 9(4), 829-840
CODEN: EOIDER; ISSN: 1354-3784

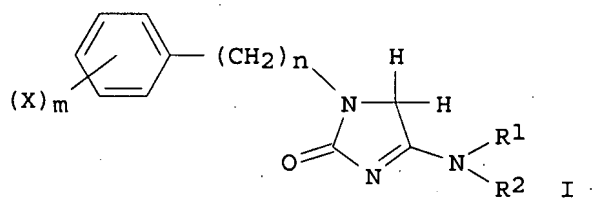
PY 2000

L2 ANSWER 7 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Imidazolinone derivatives for treatment of anxiety and tension

IN Rostock, Angelika; Dost, Rita; Tober, Christine; Bartsch, Reni; Unverferth, Klaus; Rundfeldt, Chris

GI



I

AB A process for the treatment of anxiety and tension comprises administering to a patient in need therefor an anxiolytically effective amount of I (X = H, C1-4 alkyl, C1-4 alkoxy, CF3, halo; R1, R2 = C1-4 alkyl, cycloalkyl, C2-4 hydroxyalkyl, heteroalkyl, or R1 and R2 together form C2-6 alkylene

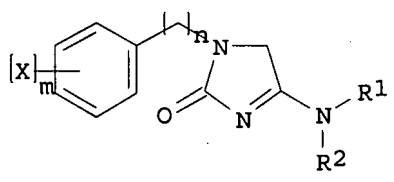
in which one CH2 can be replaced by O, N, or S; n = 0, 1; m = 0-5) or a pharmaceutically acceptable salt thereof.
SO U.S., 8 pp.
CODEN: USXXAM
PY 1999
1998

L2 ANSWER 8 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI New anti-epileptic drugs
AU Walker, Matthew C.; Sander, Josemir W.
AB A review with 78 refs. Epilepsy represents the most common serious neurol. disorder, with a prevalence of 0.4-1%. Approx. 30% of patients are resistant to currently available drugs. New anti-epileptic drugs are needed to treat refractory epilepsy, improve upon current therapies, improve the prognosis of epilepsy and to prevent the epileptogenic process. Designing compds. with specific physiol. targets would seem the most rational method of anti-epileptic drug development, but results from this approach have been disappointing; the widespread screening of compds. in animal models has been much more fruitful. Older methods of animal screening have used acute seizure models, which bear scant relationship to the human condition. More modern methods have included the development of animal models of chronic epilepsy; although more expensive, it is likely that these models will be more sensitive and more specific in determining anti-epileptic efficacy. In this review, we consider the possible physiol. targets for anti-epileptic drugs, the animal models of epilepsy, problems with clin. trials and ten promising anti-epileptic drugs in development (AWD 131-138, DP16 (DP-VPA), ganaxolone, levetiracetam, losigamone, pregabalin, remacemide, retigabine, rufinamide and soretolide). Perhaps the most important advances will come about from the realization that epilepsy is a symptom, not a disease. Preclin. testing should be used to determine the spectrum of epilepsies that a drug can treat, and to direct later clin. trials, which need to select patients based on carefully defined epilepsy syndromes and etiologies. Not only will such an approach improve the sensitivity of clin. trials, but also will lead to a more rational basis on which to treat.
SO Expert Opinion on Investigational Drugs (1999), 8(10), 1497-1510
CODEN: EOIDER; ISSN: 1354-3784
PY 1999

L2 ANSWER 9 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Progress report on new antiepileptic drugs: a summary of the fourth Eilat conference (EILAT IV)
AU Bialer, M.; Johannessen, S. I.; Kupferberg, H. J.; Levy, R. H.; Loiseau, P.; Perucca, E.
AB A review with .apprx.65 refs. The Fourth Eilat Conference on New Antiepileptic Drugs (AEDs) was held at the Royal Beach Hotel, Eilat, Israel, from 6th to 10th Sept. 1998. Epileptologists and scientists from 20 countries attended the conference, which was held to discuss a number of issues in drug development, including outcome assessment in epilepsy (long-term efficacy, quality of life, safety), cost-effectiveness, an update on drugs in development, a progress report on recently marketed AEDs, and controversies in strategies for drug development. This review focuses on drugs in development and recently marketed AEDs. Drugs in development include ADCI, AWD 131-138, DP16, ganaxolone (CCD 1042), levetiracetam (ucb L059), losigamone, pregabalin (iso-Bu GABA [CI-1008]), remacemide hydrochloride, retigabine (D-23129), rufinamide (CGP 33101), soretolide (D2916), TV1901, and 534U87. New information on the safety and efficacy of recently marketed drugs (felbamate, fosphenytoin, gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide) and of a new antiepileptic device, the neurocybernetic prosthesis (NCP), has become available. This paper summarizes the presentations made at the conference.
SO Epilepsy Research (1999), 34(1), 1-41
CODEN: EPIRE8; ISSN: 0920-1211

PY 1999

L2 ANSWER 10 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Preparation of anticonvulsive 1-ar(alk)ylimidazolin-2-ones
IN Lankau, Hans-Joachim; Menzer, Manfred; Unverferth, Klaus; Gewald, Karl; Schafer, Harry
GI



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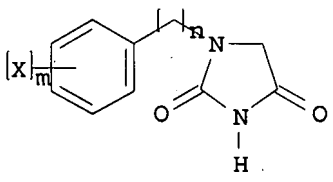

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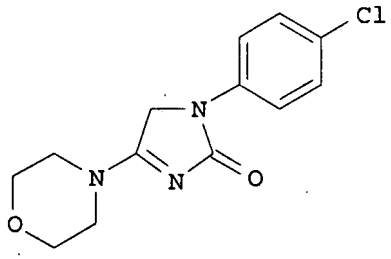

III

AB The title compds. [I; X = H, C1-4 alkyl, C1-4 alkoxy, etc.; R1, R2 = C1-4 alkyl, C2-4 hydroxyalkyl, C3-10 cycloalkyl; R1R2 = C2-6 alkylene residue in which CH2 group is optionally replaced by O, N or S; n = 0-1; m = 0-5], useful for treating an epileptic disorders, were prepared by reacting imidazolinedione II with a secondary amine HNR1R2. E.g., the title compound III showed ED50 (p.o) of 21 mg/kg for the maximum electroshock, ED50 of 16 mg/kg in the s.c. pentetrazole test, and NT50 for neurotoxicity of > 400 mg/kg.
SO U.S., 5 pp., Cont.-in-part of U.S. Ser. No. 708,665, abandoned.
CODEN: USXXAM
PY 1999
1997

=> s idiopathic(n)epilepsy
L4 1894 IDIOPATHIC(N) EPILEPSY

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(FILE 'HOME' ENTERED AT 14:49:19 ON 06 AUG 2007)

FILE 'REGISTRY' ENTERED AT 14:49:36 ON 06 AUG 2007
E "AWD 131-138"/CN 25
L1 1 S E3

FILE 'CAPLUS, BIOSIS, MEDLINE, EMBASE' ENTERED AT 14:50:43 ON 06 AUG 2007
L2 51 S AWD(A)131-138 OR IMEPITOIN OR 188116-07-6
L3 28 DUP REMOVE L2 (23 DUPLICATES REMOVED)
L4 1894 S IDIOPATHIC(N)EPILEPSY

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L5 1 L2 AND L4

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L5 ANSWER 1 OF 1 MEDLINE on STN

TI Anticonvulsant activity and tolerance of ELB138 in dogs with epilepsy: a clinical pilot study.

AU Rieck Susanne; Rundfeldt Chris; Tipold Andrea

AB A new antiepileptic and anxiolytic drug, ELB138, was evaluated in a clinical pilot study in dogs with newly diagnosed or chronic idiopathic epilepsy. The purpose was to verify clinically the anticonvulsant effectiveness of this substance, which had already been demonstrated experimentally. Data from 29 dogs treated with ELB138 were compared with results obtained retrospectively from 82 dogs treated with conventional antiepileptic medication. The reduction in seizure frequency using ELB138 in dogs with newly diagnosed idiopathic epilepsy was comparable to the reduction in dogs treated either with phenobarbital or primidone. In dogs with chronic epilepsy and add-on therapy with either ELB138 or potassium bromide, such supplementation reduced the seizure frequency and the duration and severity of seizures. The most obvious difference between ELB138 treatment and conventional medications became clear in the evaluation of side effects, which in those dogs treated with ELB138 were rare, and consisted mostly of transient polyphagia. This pilot study confirmed that ELB138 has a potent anticonvulsant effect in dogs with idiopathic epilepsy. These results will form the basis for a multicentre, blinded study.

SO Veterinary journal (London, England : 1997), (2006 Jul) Vol. 172, No. 1, pp. 86-95.
Journal code: 9706281. ISSN: 1090-0233.

PY 2006

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AT 15:26:57 ON 06 AUG 2007
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COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                49.85      57.86

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                -7.80      -7.80

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     (FILE 'HOME' ENTERED AT 14:49:19 ON 06 AUG 2007)

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                E "AWD 131-138"/CN 25
L1            1 S E3

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L2           51 S AWD(A)131-138 OR IMEPITOIN OR 188116-07-6
L3           28 DUP REMOVE L2 (23 DUPLICATES REMOVED)
L4         1894 S IDIOPATHIC(N)EPILEPSY
L5            1 S L2 AND L4

=> d ti au abs so py 11-20 l2

L2   ANSWER 11 OF 51  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Use of 1-ar(alk)ylimidazolin-2-ones for treating anxiety and stress
     conditions
IN   Rostock, Angelika; Dost, Rita; Tober, Christine; Bartsch, Reni;
     Unverferth, Klaus; Rundfeldt, Chris
GI
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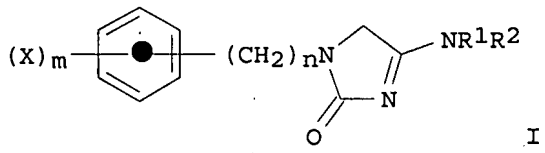

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AB   The title compds. (I; X = H, C1-4 alkyl or alkoxy, CF3, halo; R1, R2 =
     C1-4 alkyl, cycloalkyl, heteroalkyl, or R1 and R2 together = C2-6 alkylene
     in which 1 CH2 group may be substituted by O, N, or S; m = 0-5; n = 0, 1)
     and their pharmaceutically acceptable salts are effective in treatment of
     anxiety and stress without sedative side effects.  This was demonstrated
     by the decrease in conflict avoidance behavior in mice induced by
     1-(4-chlorophenyl)-4-morpholinoimidazolin-2-one (3-10 mg/kg orally).  I
     showed little pharmacol. interaction with EtOH and little neurotoxicity.
SO   Ger. Offen., 10 pp.
     CODEN: GWXXBX
PY   1998
     1998
     2006
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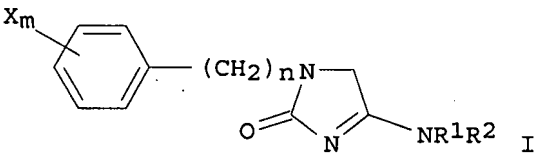
L2 ANSWER 12 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI AWD 131-138 as anxiolytic anticonvulsant
AU Rostock, A.; Tober, C.; Dost, R.; Rundfeldt, C.; Bartsch, R.; Egerland, U.; Stark, B.; Schupke, H.; Kronbach, T.; Lankau, H. -J.; Unverferth, K.; Engel, J.
AB A review with 3 refs. on the synthesis and pharmacol. of the title anticonvulsant.
SO Drugs of the Future (1998), 23(3), 253-255
CODEN: DRFUD4; ISSN: 0377-8282
PY 1998

L2 ANSWER 13 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI The antiepileptic drug AWD 131-138 stimulates different recombinant isoforms of the GABAA receptor through the benzodiazepine binding site
AU Sigel, Erwin; Baur, Roland; Netzer, Rainer; Rundfeldt, Chris
AB Recombinant γ-aminobutyric acid A (GABAA) receptors of the subunit compns. α1β2γ2, α1β3γ2, α2β2γ2, α3β2γ2 and α5β2γ2 were expressed in Xenopus oocytes in a functionally active form. At all subunit combinations, AWD 131-138 dose-dependently stimulated GABA currents. At 10 μM AWD 131-138, this allosteric stimulation amounted in average to about 12-21% of the maximal stimulation achieved using diazepam. The threshold of stimulation was about 0.3-1.0 μM. One micrometer of the benzodiazepine antagonist flumazenil (Ro 15-1788) counteracted the current stimulation by 10 μM AWD 131-138, indicating that this drug acts at the binding site for benzodiazepines.
SO Neuroscience Letters (1998), 245(2), 85-88
CODEN: NELED5; ISSN: 0304-3940
PY 1998

L2 ANSWER 14 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Preparation of 4-amino-1-aralkylimidazolones as anticonvulsants.
IN Lankau, Hans-Joachim; Menzer, Manfred; Unverferth, Klaus; Gewald, Karl; Schaefer, Harry

GI



AB Title compds. [I; X = H, alkyl, alkoxy, CF3, halo; R1, R2 = alkyl, cycloalkyl, heteroalkyl; R1R2 = alkylene optionally interrupted by O, N, or S; n = 0, 1; m = 0-5], were prepared Thus, 1-(4-chlorophenyl)-4-piperidinoimidazolin-2-one (general preparative methods given) at 100 mg/kg in rats gave 100% inhibition of maximal electroshock-induced convulsions.

SO Ger. Offen., 7 pp.
CODEN: GWXXBX

PY 1997
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L2 ANSWER 15 OF 51 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

TI Anticonvulsant efficacy of the low-affinity partial benzodiazepine receptor agonist ELB 138 in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures.

AU Loescher, Wolfgang [Reprint Author]; Potschka, Heidrun; Rieck, Susanne; Tipold, Andrea; Rundfeldt, Chris

AB Purpose:Ataxia, sedation, amnesia, ethanol and barbiturate potentiation, loss of efficacy (tolerance), development of dependence, and the potential for drug abuse limit the clinical use of benzodiazepines (BZDs) for long-term treatment of epilepsy or anxiety. BZD ligands that are in

current use act as full allosteric modulators of gamma-aminobutyric acid (GABA)-gated chloride channels and, on long-term administration, trigger a functional uncoupling between the GABAA and BZD recognition sites. Partial allosteric modulators, which have a low intrinsic activity at the BZD recognition site of the GABAA receptor, might eventually overcome the limitations of full agonists such as diazepam (DZP). Methods: In the present study, the new low-affinity partial BZD-receptor agonist ELB 138 (former name AWD 131-138; 1-(4-chlorophenyl)-4-morpholino-imidazolin-2-one) was evaluated in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures. Results: ELB 138 was shown to increase potently the pentylenetetrazole (PTZ) seizure threshold in dogs. Prolonged oral administration with twice-daily dosing of ELB 138 with either 5 or 40 mg/kg over a 5-week period was not associated with loss of anticonvulsant efficacy in the PTZ dog model. To study whether physical dependence developed during long-term treatment, the BZD antagonist flumazenil was injected after 5 weeks of treatment with ELB 138. Compared with prolonged treatment with DZP, only relatively mild abstinence symptoms were precipitated in dogs treated with ELB 138, particularly at the lower dosage (5 mg/kg, b.i.d.). In a prospective trial in dogs with newly diagnosed epilepsy, ELB 138 markedly reduced seizure frequency and severity without significant difference to standard treatments (phenobarbital or primidone) but was much better tolerated than the standard drugs. In dogs with chronic epilepsy, most dogs exhibited a reduction in seizure frequency and severity during add-on treatment with ELB 138. Conclusions: The data demonstrate that the partial BZD receptor agonist ELB 138 exerts significant anticonvulsant efficacy without tolerance in a dog seizure model as well as in epileptic dogs with spontaneously recurrent seizures. These data thus substantiate that partial agonism at the BZD site of GABAA receptors offers advantages versus full agonism and constitutes a valuable approach for treatment of seizures.

SO Epilepsia, (October 2004) Vol. 45, No. 10, pp. 1228-1239. print. ISSN: 0013-9580 (ISSN print).
PY 2004

L2 ANSWER 16 OF 51 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

TI Evaluation of the novel antiepileptic drug, AWD 131-138, for benzodiazepine-like discriminative stimulus and reinforcing effects in squirrel monkeys.

AU Yasar, Sevil [Reprint Author]; Bergman, Jack; Munzar, Patrik; Redhi, Godfrey; Tober, Christine; Knebel, Norbert; Zschiesche, Michael; Paronis, Carol

AB AWD 131-138 (1-(4-chlorophenyl)-4-morpholino-imidazolin-2-one), a new low-affinity partial benzodiazepine receptor agonist with potent anticonvulsant and anxiolytic properties in rodent models, was studied in squirrel monkeys trained to discriminate intramuscular (i.m.) injections of midazolam (0.3 mg/kg) from injections of vehicle. Diazepam produced midazolam-like responding at cumulative doses of 1.0 and 3.0 mg/kg i.m. and decreased rates of responding at 3.0 mg/kg (plasma levels of about 400 ng/ml). In contrast, AWD 131-138 did not produce midazolam-like responding or alter response rates at cumulative doses up to 18.0 mg/kg i.m. (plasma levels over 2100 ng/ml). Other monkeys were trained to intravenously (i.v.) self-administer cocaine (56.0 mug/kg/injection). When AWD 131-138 (10-100 mug/kg/injection) was studied by substitution, responding declined to vehicle substitution levels within three sessions. At the dose of 100 mug/kg i.v. AWD 131-138, sufficient drug was self-administered during the first session (about 3.5 mg/kg) to produce plasma levels above 1000 ng/ml, yet responding over the next two sessions dropped to vehicle levels. The failure of AWD 131-138 to produce benzodiazepine-like discriminative effects and the absence of drug self-administration behavior when substituted for cocaine suggest that its

abuse liability is low.
SO European Journal of Pharmacology, (4 April 2003) Vol. 465, No. 3, pp. 257-265. print.
ISSN: 0014-2999 (ISSN print).
PY 2003

L2 ANSWER 17 OF 51 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
TI New antiepileptic drugs currently in clinical trials: Is there a strategy in their development?.
AU Bialer, Meir [Reprint author]
AB In designing and developing antiepileptic drugs (AEDs), attention should be paid to the desirable pharmacokinetic properties of potential new agents so that molecules are designed to achieve the desired pharmacodynamic and pharmacokinetic profiles. A review of current compounds in development or in clinical trials shows that several promising agents have incorporated pharmacokinetic-based design into their development process. This is particularly true for new AEDs that are second-generation or follow-up compounds of existing AEDs.
SO Therapeutic Drug Monitoring, (February, 2002) Vol. 24, No. 1, pp. 85-90. print.
CODEN: TDMODV. ISSN: 0163-4356.
PY 2002

L2 ANSWER 18 OF 51 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
TI Analytical data and physicochemical properties of 1-(4-chlorphenyl)-4-morpholino-imidazolin-2-one, AWD 131-138.
Original Title: Identitaet und physikochemische Eigenschaften von 1-(4-Chlorphenyl)-4-morpholino-imidazolin-2-on, AWD 131-138.
AU Heinecke, K.; Thiel, W. [Reprint author]
AB The structure of the anticonvulsant 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazolin-2-one (Code: AWD 131-138, CAS-Number: 188116-07-6) was proved by IR, UV, 1HNMR, 13CNMR and mass spectra. AWD 131-138 is practically insoluble in a neutral aqueous medium at 20 degreeC (S apprx 0.08 g/l). The solubility of the substance in 0.1 N HCl is about 2.7 g/l. In DMF, AWD 131-138 is sparingly soluble (S apprx 28.5 g/l). The pKa-value is about 2.5. The partition coefficients P = COctanol/Cwater at 37 degreeC range from 0.7 at pH apprx 1 to about 20 at pH gtoreq 6.
SO Pharmazie, (June, 2001) Vol. 56, No. 6, pp. 458-461. print.
CODEN: PHARAT. ISSN: 0031-7144.
PY 2001

L2 ANSWER 19 OF 51 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
TI Effect of AWD 131-138 in a model for focal epilepsy, the amygdala kindling in rats.
AU Tober, Christine [Reprint author]; Stark, Barbara [Reprint author]; Bartsch, Reni [Reprint author]; Kronbach, Thomas [Reprint author]
SO Epilepsia, (2000) Vol. 41, No. Supplement 7, pp. 53. print.
Meeting Info.: Annual Meeting of the American Epilepsy Society. Los Angeles, CA, USA. December 01-06, 2000. American Epilepsy Society.
CODEN: EPILAK. ISSN: 0013-9580.
PY 2000

L2 ANSWER 20 OF 51 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
TI Progress report on new antiepileptic drugs: A summary of the Fifth Eilat Conference (EILAT V).
AU Bialer, M. [Reprint author]; Johannessen, S. I.; Kupferberg, H. J.; Levy, R. H.; Loiseau, P.; Perucca, E.

AB The Fifth Eilat Conference on New Antiepileptic Drugs (AEDs) took place at the Dan Hotel, Eilat, Israel, 25-29 June 2000. Basic scientists, clinical pharmacologists and neurologists from 20 countries attended the conference, whose main themes included recognition of unexpected adverse effects, new indications of AEDs, and patient-tailored AED therapy. According to tradition, the central part of the conference was devoted to a review of AEDs in development, as well to updates on AEDs that have been marketed in recent years. This article summarizes the information presented on drugs in preclinical and clinical development, including AWD 131-138, DP-valproate, harkoseride, LY300164, NPS 1776, NW 1015, pregabalin, remacemide, retigabine, rufinamide and valrocemide. The potential value of an innovative strategy, porcine embryonic GABAergic cell transplants, is also discussed. Finally, updates on felbamate, fosphenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide, and the antiepileptic vagal stimulator device are presented.

SO Epilepsy Research, (January, 2001) Vol. 43, No. 1, pp. 11-58. print.
CODEN: EPIRE8. ISSN: 0920-1211.
PY 2001

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